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<b>(54) Title:</b> METHODS FOR PREDICTING DRUG RESPONSE  <b>(57) Abstract</b>  Methods are provided for predicting the response of a subject to a drug or treatment regimen. The predictive measurement is used with biochemical parameters obtained from a subject to predict whether that subject will respond to the particular drug or treatment regimen. Predictive methods may also be used to determine the equivalence of different dosages of a drug.		

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## METHODS FOR PREDICTING DRUG RESPONSE

### TECHNICAL FIELD OF THE INVENTION

This invention relates to methods for predicting the responsiveness of a subject to a particular drug or treatment regimen.

### BACKGROUND OF THE INVENTION

The variability of individual responses to drugs can complicate the treatment of many disorders. Even within a population that is relatively homogenous (*i.e.*, same sex, a narrow range of ages, etc.), some subjects will respond well to a particular drug, while other subjects will respond poorly.

The problem of interpatient variability is particularly serious among sufferers of chronic diseases. For example, many drugs utilized to treat chronic psychological disorders (*e.g.*, depression) require many days or even weeks before an effect, if any, is seen. For subjects that do not respond to the drug, the "wait and see" period only prolongs the period of suffering.

U.S. Patent No. 5,209,920 discloses a method for predicting susceptibility to inflammatory diseases. The method disclosed involves administering a test compound which is known to affect the hypothalamic-pituitary-adrenal axis, then measuring the levels of pituitary and adrenal hormones. Individuals that do not respond to the test compound with increased pituitary and adrenal hormones are deemed "susceptible." This disclosure does not provide any teaching regarding a method for predicting whether a subject will respond to a particular drug or treatment regimen.

Accordingly, there is a need in the art for a method of predicting the responsiveness of a subject to a particular drug or treatment regimen. A method for predicting responsiveness would allow physicians and other medical professionals to quickly determine an effective drug or treatment regimen for a particular subject, thus reducing the subject's suffering and expense. A method for predicting responsiveness would also reduce or eliminate a subject's exposure to drugs or treatment regimens that are not effective, thereby reducing or eliminating suffering from side effects of such ineffective drugs or treatment regimens.

### DETAILED DESCRIPTION OF THE INVENTION

It is an object of this invention to provide methods for predicting a subject's responsiveness to a drug or treatment regimen. It is yet a further object of the instant invention to provide methods for predicting a subject's responsiveness to a administration of recombinant human insulin-like growth factor I (rhIGF-I) or IGF-I complexed with insulin-like growth factor binding protein 3 (IGFBP-3).

It is a further object of the instant invention to provide methods and diagnostic kits for predicting a subject's responsiveness to a drug or treatment regimen.

It is another object of the instant invention to provide methods for determining the equivalence of different dosages of a drug for any given response. These methods allow the selection of dosage based on relatively small patient numbers, reducing the time and expense of "dose-ranging" clinical studies.

### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a correlation density plot for biochemical parameters from clinical trial 9602. Bold face indicates responses that are statistically significant. Abbreviations used: "nd" means not determined; "IGF-I" means insulin-like growth factor I; "IGF-II" means insulin-like growth factor II; "IGFBP-2" means insulin-like growth factor binding protein 2; "IGFBP-3" means insulin-like growth factor binding protein 3; "LH" means leutinizing hormone; "EPO" means erythropoietin; "C1CP" means procollagen peptide; "PTH" means parathyroid hormone; "BSAP" means bone specific alkaline phosphatase; "A4" means androstenedione; "DHEA-S" means dehydroepiandrosterone sulfate; "T3" means triiodothyronine; "T4" means tetraiodothyronine; "CBG" means cortisol binding globulin; and "SHBG" means steroid hormone binding globulin.

Figure 2 shows a correlation density plot for biochemical parameters from clinical trial 9604. Bold face indicates responses that are statistically significant. Abbreviations are the same as in Figure 1.

Figure 3 shows correlations between biochemical responses to administration of IGF-I/IGFBP-3 complex. Panel A shows IGF-I response versus IGFBP-3 response. Panel B shows estradiol response versus IGF-I response. Panel C shows estradiol response versus C1CP response.

Figure 4 shows a crude predictive relationship plotted using data from 9602 clinical trial data. The predictive method used was the product of the log[TSH] and total T4.

Figure 5 shows a plot of predicted versus actual responses using 9602 clinical trial data. The predictive method used is shown in Example 1.

5        Figure 6 is a plot of predicted versus actual responses using 9604 clinical trial data. The predictive method used is exemplified in Example 1.

Figure 7 shows plots of predicted versus actual responses for grip strength (GS) using 9606 clinical trial data. Panel A shows low dose (0.5 mg/kg/day, squares) and high dose (1 mg/kg/day, diamonds) responses and a plot of the predicted responses calculated using Formula #1. Panel B shows low dose and high dose responses and a plot of the predicted responses using Formula #1-2.

10        Figure 8 shows plots of predicted versus actual responses for fat body mass (FBM) and hip bone mineral density (BMD) using 9606 clinical trial data. Panel A shows low dose (0.5 mg/kg/day, squares) and high dose (1 mg/kg/day, diamonds) responses and a plot of the predicted responses for FBM using Formula #1-3. Panel B shows low dose (0.5 mg/kg/day, squares) and high dose (1 mg/kg/day, diamonds) responses and a plot of the predicted responses for BMD using Formula #2.

#### MODES OF CARRYING OUT THE INVENTION

20        The invention relates to methods for predicting a subject's response to a particular drug or treatment regimen. A subject's biochemical profile (*e.g.*, serum concentrations of thyroid, adrenal, gonadal and pituitary hormones, organ-specific markers and the like) is measured prior to treatment and used to predict the subject's response to a particular drug or treatment regimen.

25        Not all subjects respond identically to any given drug or treatment regimen. For most, if not all drug and treatment regimens, subjects respond in varying degrees, and some percentage of the subjects fail to respond entirely. A method for predicting a particular subject's response to a particular drug or treatment regimen has been discovered.

30        Also included within the instant invention are diagnostic kits utilizing a predictive method in accordance with the invention.

Different subjects diagnosed with a given disorder generally exhibit widely varying biochemical profiles. The response of an individual to a drug is dependent on that individual's neuroendocrine status that, in turn, is reported by some aspect of the individual's biochemical profile. However, because the interactions between the different biochemical and endocrine sub-systems (*e.g.*, between the somatotrophic, thyroid and adrenal axes) are extremely complex, it is necessary to look at a large number of biochemical markers before devising a predictive method. The methods of the invention, therefore, utilize a broad biochemical profile to predict whether a given subject will respond to a particular drug or treatment regimen.

The methods within the instant invention are not based on intuitive logic but rather are based on analyzing the effect of a drug or treatment regimen on known biochemical and/or endocrine elements.

A specific predictive method of the invention may be utilized to predict the responsiveness of a subject to a particular drug or treatment regimen. The particular biochemical values that are utilized in the predictive method are measured in the subject, then employed in the predictive method. As shown in Example 2, serum levels of TSH, total T4, SHBG and IGF-I are used to create a predictive method to determine the effect of the administration of IGF/IGFBP-3 complex on a subject's fat body mass, grip strength or bone mineral density. A physician or other skilled artisan may then utilize this predicted response value to decide whether or not to treat the subject with IGF/IGFBP-3 complex in order to affect the subject's fat body mass, grip strength and/or bone mineral density. The following formulas are provided for predicting a subject's response:

$$PE_{GS} \text{ or } PE_{FBM} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I]},$$

$$PE_{GS} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I] \times [C1CP]},$$

$$PE_{BMD} = \frac{[C1CP] \times [tT4]}{[tT3] \times [cort]}, \text{ and}$$

$$PE_{FBM} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I] \times [tT3]}.$$

The predictive methods of the invention may also be used to provide diagnostic kits. A diagnostic kit based on a predictive method formulated in accordance with methods of the invention includes reagents for measuring the biochemical parameters that

are utilized in the predictive method. Reagents for measuring biochemical parameters are well known in the art, and may include enzyme-linked immunosorbent assays (ELISA), radioimmunoassays (RIA), biosensors and/or any other assays known in the art for specific detection of the level of a particular biochemical parameter.

5           Biosensors are particularly advantageous for use in a kit. Generally, a biosensor is a device which utilizes a specific binding partner of the analyte (such as an antibody or receptor molecule) to capture the analyte, producing an optical or electrical alteration in the device. For example, the AMBRInstitute (Australian Membrane and Biotechnology Research Institute) has developed a biosensor which utilizes lipid bilayer membrane  
10           containing gramicidin ion channels and antibodies specific to the analyte (the presence of an analyte is detected by changes in impedance across the membrane). IA, Inc., has developed fiber optic sensors utilizing evanescent field technology. Quantech, Inc. is developing biosensors using surface plasmon resonance to detecting binding between an analyte and a receptor (binding is signaled by a shift in the wavelength of light absorbed by  
15           the device). Multiple biosensors may be fabricated in a single unit, such that all of the required measurements may be accomplished with a single device. Utilizing such a device, the values for all biochemical parameters necessary for a calculating a predictive relationship can be determined simultaneously.

          Such a diagnostic kit also optionally includes instructions, software, and/or a  
20           worksheet for calculating the predicted responsiveness, based on the particular biochemical parameters tested. Alternately, particularly in the case of kits utilizing biosensors for measurement of biochemical parameters, the biosensor devices may be read using an instrument includes (or is linked to) a digital computer with software to calculate a predicted response utilizing the biochemical parameters required for the calculation of the  
25           particular predictive relationship.

          Instructions for the kit include a listing of required materials and assay results, a mathematical representation of the predictive relationship, and a protocol for utilizing the biochemical parameter(s) with the mathematical representation to produce a predicted responsiveness. Software included with the kit operates on a digital computer, prompts the  
30           user for the necessary biochemical parameters or receives the biochemical parameters from the measuring device, and, using the predictive method, calculates and returns the predictive responsiveness. A worksheet for the kit includes a mathematical representation

of the predictive method, and allows the user to calculate the predicted responsiveness based on the biochemical parameters obtained using the assays in the kit.

5 The instant invention also provides methods for determining when dose response is saturated for a particular drug effect (*i.e.*, determining whether a first dosage and a second dosage of a drug are equivalent in effect). These methods are particularly advantageous because they can be used to predict dose response saturation with relatively small numbers of subjects. This can greatly reduce the time and expense of the clinical studies needed to determine the proper dosage of a candidate drug ("dose-ranging studies"). It is preferable that drug dosages be set no higher than the level that achieves the maximum effect.

10 Delivery of excess drug is uneconomical and can lead to adverse effects due to the excess drug dose.

The methods for determining saturation of dose response to a drug utilize a predictive method derived as described herein. At least two different dosages of the drug are administered to groups of test subjects. Biochemical markers are assayed before

15 administration of the drug, and actual responses are measured after administration of the drug. Predicted responses are then calculated using a predictive relationship created in accordance with the instant invention. Predicted responses and actual responses can then be utilized as the data sets for linear regression analysis.

One of the predictive relationships disclosed herein may be utilized, or a new

20 predictive relationship may be formulated and used to determine if a drug dose is saturating for a given response.

The invention also relates to methods for formulating predictive models for responsiveness to a particular drug or treatment regimen. A predictive method may be created for any particular drug or treatment regimen. The method for formulating

25 predictive models involves:

- (a) selecting a cohort of test subjects;
- (b) obtaining an biochemical profile from each of the test subjects by measuring various biochemical parameters;
- (c) administering a particular drug or treatment regimen;
- 30 (d) measuring the effects of the drug or treatment regimen;
- (e) performing correlation tests between the biochemical parameters and the effects of the drug or treatment regimen;



- (f) selecting biochemical parameters that correlate with the effects of the drug or treatment regimen; and
- (g) deriving a predictive method between the selected biochemical parameters and the response to the drug or treatment regimen.

5 In the method for formulating a predictive model for predicting a subject's response, a cohort is selected by criteria known to one of skill in the art. Preferably, the cohort is approximately representative of the population for which the drug or treatment regimen is intended.

10 A biochemical profile is determined by measuring serum levels of various biochemical molecules and other serum markers. A biochemical profile should include measurements of biochemical molecules and serum markers from a wide variety of endocrine and metabolic systems. Preferably, a biochemical profile will include measurements of biochemical parameters selected from a wide variety of endocrine systems, including, but not limited to, the somatotrophic axis (*e.g.*, IGF-I, IGF-II, IGFBP-3, 15 growth hormone (GH) and the like), the thyroid axis (triiodothyronine (T3), tetraiodothyronine (T4), thyroid stimulating hormone (TSH), thyroglobulin, and the like), the adrenal axis (dehydroepiandrosterone -(DHEA), dehydroepiandrosterone-sulfate (DHEAS), cortisol, aldosterone, and the like), the gonadal axis (testosterone, androstenedione, estradiol, and the like), and the hypothalamic-pituitary axis (prolactin 20 (PRL), leutinizing hormone (LH) and the like). A biochemical profile may also optionally include serum levels of markers specific to certain processes or organ systems, including parameters including, but not limited to, levels of anabolic markers (such as procollagen peptide (C1CP) and the like), bone markers (such as osteocalcin, bone alkaline phosphatase, and the like) and renal hormones (such as renin, angiotensin, and the like).

25 Administration of the test drug or treatment regimen may begin following acquisition of samples sufficient to perform all testing necessary to establish a biochemical profile for each member of the test cohort. The drug or treatment regimen may be administered to the test cohort in any manner that is known in the art; the exact method of administration, dose level and dosing schedule will be specific to the particular drug or 30 treatment regimen, as will be apparent to one of skill in the art.

During the administration of the drug or treatment regimen, or subsequent to the administration (depending on the particular drug or treatment regimen and the response

that is to be measured), responsiveness is measured. As with the exact treatment details, the measurement of responsiveness will be specific to the particular drug or treatment regimen, as will be apparent to the skilled artisan. In the case of IGF or IGF/IGFBP-3 complex, responsiveness may be measured by testing bone markers (*e.g.*, bone mineral density, serum levels of osteocalcin, bone alkaline phosphatase and the like.), renal markers (*e.g.*, serum levels of renin, creatinine clearance, and the like), anabolic markers (such as serum levels of C1CP, nitrogen balance, lean body mass and the like), wound healing indices (such as wound closure rates and the like), psychological indices (such as improvement in cognitive or memory skills, improvement in symptoms of psychological disorders and the like), or any other indicator of responsiveness, as will be apparent to one of skill in the art. Measures of responsiveness are preferably normalized to a baseline level. The data set of the measures of responsiveness is referred to as the "efficacy set."

After a biochemical profile has been established and measures of responsiveness have been obtained for the members of the test cohort, the individual parameters of the biochemical profile are tested for correlation with the measures of responsiveness. Correlation testing may be done using any valid statistical testing method known to the art.

Biochemical parameters that correlate well (either positively or negatively) are selected for use in deriving the predictive method. It is preferable to begin investigating the three or four biochemical parameters with the highest *r* values. Preferably, biochemical parameters that correlate with an *r* value of greater than 0.4 are selected for use in deriving the predictive method. The selected biochemical parameters are then combined to derive the predictive method. In generating a predictive method, operations such as addition, subtraction, product, ratio, and the like should be performed between each pair of the selected data sets (and derivative sets representing square root, logarithm, and the like) of each should be examined, in each case comparing the resulting transformed data set with the efficacy set. Those comparisons yielding progressively higher "*r*" values are retained for further combinations, until the best possible predictive method is generated. The value of each biochemical parameter selected for use in deriving the predictive method may also be multiplied, divided, added to, or subtracted from when deriving the predictive relationship, in order to make maximize the accuracy of the predictive method. The values of each biochemical parameter selected for use in deriving the predictive method may be further modified by any standard mathematical operation, such as raising to a power,

taking a logarithm, finding a root, and the like, in order to maximize the accuracy of the predictive method.

The predicted and actual responses may be plotted or may be directly used in a linear regression analysis. The results of the linear regression analysis for the different dosages of the drug are then compared to test if the lines are similar (e.g., coincident or nearly so). Any statistical method for comparing two lines can be used to compare the results from the two different dosages. The slopes and y intercepts may be compared separately, or in a single test. One preferred method for comparing two lines is comparing the slopes and y-axis intercepts for the two lines, preferably utilizing a t-test method. Alternately, if the slopes and y intercepts are compared simultaneously, the lines are preferably compared utilizing the F distribution.

Where separate testing is employed, the t value for testing the hypothesis that the slopes of the two lines are similar may be tested by calculating according to the following equation:

$$T = \frac{(\hat{b}_1 - \hat{b}_2)}{S_p \sqrt{\frac{1}{\sum (x_{1j} - \bar{x}_1)^2} + \frac{1}{\sum (x_{2j} - \bar{x}_2)^2}}}$$

where

$$S_p = \frac{(y_{1j} - \hat{y}_{1j})^2 + (y_{2j} - \hat{y}_{2j})^2}{n_1 + n_2 - 4}$$

where subscripts 1 and 2 refer to data sets 1 and 2 (e.g., the data sets for the low dose and

$$T = \frac{a_1 - a_2}{S_{a_1 - a_2}}$$

high dose, respectively),  $1j$  is the  $j$ th observation from the data for data set 1,  $2j$  is the  $j$ th observation for data set 2,  $\hat{b}$  is the slope of the line derived from the regression of the data set,  $\bar{x}$  is the mean of the values of  $x$ , and  $\hat{y}$  is the y intercept derived from the regression of the data set. Additionally, the hypothesis that the y-intercepts of the two lines are similar may be tested by calculating the t value according to the following equation:

where

$$S_{a_1-a_2} = \sqrt{S_{p_1|y|x}^2 \left[ \frac{1}{n_1} + \frac{1}{n_2} + \frac{\bar{x}_1^2}{(n_1-1)S_{x_1}^2} + \frac{\bar{x}_2^2}{(n_2-1)S_{x_2}^2} \right]}$$

and

$$S_{p_1|y|x}^2 = \frac{(n_1-2)S_{y|x_1}^2 + (n_2-2)S_{y|x_2}^2}{n_1 + n_2 - 4}$$

where  $S_{y|x_1}^2$  and  $S_{y|x_2}^2$  are the residual mean squares of the errors for lines 1 and 2, respectively.

5 Generally, two lines will be considered similar if statistical testing demonstrates that the slopes and the y intercepts are identical with a confidence of  $p \leq 0.1$ , preferably  $p \leq 0.05$ , more preferably  $p \leq 0.025$ , even more preferably  $p \leq 0.01$ .

If the two lines are similar, then the response to the different dosages of the drug are equivalent, and therefore response has at least reached a plateau, and may be  
10 maximized. If the lines are not similar, then the two dosages are not equivalent.

The application of this method is shown in Figure 7(B), where Formula #1-2 of the instant invention was used to plot predictions of change in grip strength (GS) in response to administration of a low (0.5 mg/kg/day) and high (1 mg/kg/day) doses of rhIGF-I/IGFBP-3). Linear regression analysis was performed on the two sets of data points and  
15 the resulting lines were plotted. The results of linear regression analysis of the low and high doses are very similar and nearly superimposed on each other. This indicates that for the administration of rhIGF-I/IGFBP-3, response in terms of grip strength is identical for low and high doses of this particular drug. However, as shown in Figure 8(B), the high and low dosages of rhIGF-I/IGFBP-3 are not equivalent with respect to hip bone mineral  
20 density. Linear regression analysis was not performed on the data set for the low dose because the correlation value was too low ( $r < 0.4$ ). Here the results of linear regression analysis of low and high doses indicates that these doses are not equivalent.

EXAMPLESExample 1

Data sets from two separate clinical trials of rhIGF-I/IGFBP-3 complex were utilized to create a predictive method for response to the complex. The first study ("9602") involved repeated intravenous administration of rhIGF-I/IGFBP-3 to normal volunteers (male and female), ages 20-53. The second trial ("9604") involved continuous subcutaneous infusion of rhIGF-I/IGFBP-3 complex to normal female volunteers, ages 55-70.

Biochemical profiles were determined for each test subject by assaying serum levels of biochemical parameters. The effects of inter-subject variability on the analysis was minimized by calculating the biochemical response of each subject on a relative basis. For each biochemical marker, the level at the end of the study was compared with that at the beginning, then expressed as a percentage of baseline. Statistical methods, including measures of significance were applied to these data sets.

The relative IGF-responsiveness of each subject (with respect to each of the biochemical markers, especially IGF-I, IGF-II, IGFBP-2, IGFBP-3, DHEAS, androstenedione, estradiol, total T4, and procollagen peptide (C1CP)) was then computed by comparison with the mean for each treatment group. These data sets are shown in Table 1 (9602) and Table 2 (9604).

TABLE I

SUBJECTS	IGF-1 resp	IGF-II resp	BP-2 resp	BP-3 resp	CICP resp	Osteo resp	BSAP resp	EPO resp	A.Renin res	LH resp	SHBG re	PRL resp
2	88.7	103	101	93.7	89	65	113.1	111.8	61	187.8	100	111.9
3	102	88.1	115	86.5	107	187.5	87.9	78.6	70.7	63.4	101.1	67.3
4	119.3	100	112	124.3	107	68.1	100.9	82.7	74.8	28.1	106.7	122.8
6	90.7	110.5	73	96.4	97	78.8	96.3	126.8	194.3	122	91	99
7	109.8	89.7	64	94.5	105	94.4	101	98	94.6	62.2	99	108.1
8	70.7	94.8	94	95.6	87	54.2	101.9	60.4	47.9	205.8	120.8	109.9
11	125.6	98.3	103	109.9	116	112.5	88.5	81.7	129.2	72.3	90.1	90.1
12	92.9	113.8	141	100	92	136.1	106.7	159.9	113.9	116	89.1	92.8
14	91.6	104.8	177	84.7	104	100.8	109	100	85.3	112	104.7	66.7
15	92.1	111.9	30	124.2	113	96	93	93.5	125.7	88	70.1	124.3
16	115.8	83.3	93	90.3	83	102.4	98	107.2	89.9	n.d.	126	112.3
SUBJECTS	tT4 resp	FT4resp	TG resp	TBG resp	tT3 resp	DHEAS re	DHEA res	A4 resp	Testost re	CBG resp	Cort resp	Estrad resp
2	98	97.8	117.6	100	101.2	90	87.1	205	98.9	97.9	79.1	77.7
3	115	121.5	108.4	80.2	90.7	113	68.3	52	105.6	108.3	53.3	55.3
4	97	107.5	98.3	126.4	109.3	106	136.6	71	98.9	104.2	139.1	86.6
6	88	74.2	80.7	93.4	98.8	91	105.9	76	94.4	89.6	127.6	181
7	97	119.6	129.6	117.4	102.2	102	94.5	109	124.4	112.9	129.2	131.5
8	88	98	84.3	86.2	94.6	102	95.6	65	118.9	99	97.9	77.8
11	101	93.1	75.7	88.1	106.5	82	109.9	65	64.5	95	74	62
12	113	88.2	110.4	108.3	95.7	113	100	157	129.9	93.1	100	129.6
14	87	108	84.8	140.1	108.1	99	84.7	109	82.5	96.2	91.4	95.6
15	92	100.9	84.8	79	102	100	124.2	78	99	88.5	97.4	111.5
16	119	91.2	130.4	81.5	89.9	101	90.3	117	118.6	114.4	110.3	92.9

TABLE 2

SUBJECTS	EPO resp	t14 resp	TG resp	t13 resp	IGF-II resp	IGF-I resp	IGFBP3 re	C1CP resp	LH resp	PRL resp	IGFBP-1 re	IGFBP-2 resp	
5	107.5	103.5	73.1	129.6	89.7	138.3	122.7	82.9	89	52.8	132	146.2	
6	107.9	92.2	102.1	90.1	138.7	83.3	95.5	109.8	106.9	128	93.3	67.8	
7	84.5	104.3	124.8	80.4	71.7	78.5	81.7	107.3	104.1	119.1	74.8	86	
109	112	89.2	99.1	106.9	72.8	113.1	97.7	79.2	78.7	99.8	117.4	79.6	
110	75.7	111.9	74.3	93.8	90.9	115.9	109.6	146.8	122.1	86.2	73.4	111	
112	112.3	99.1	126.5	99.3	136.1	71	92.7	80.4	99.3	114.2	109.2	79.6	
201	63.4	106.2	19.1	101.4	130.6	90.9	80.8	86.4	111	140.8	64.5	111.5	
203	187.7	91.7	143.8	106.7	56.6	153.3	132.4	146.8	112.4	60.8	110.1	185.9	
204	48.9	102	137.2	92	112.9	55.8	86.0	70	76.6	98.5	125.4	43.3	
SUBJECTS	IGF-II resp	PRL resp	Estradiol re	EPO resp	Osteocal re	C1CP resp	BSAP resp	Osteocal re	Cortisol	DHEAS re	Testostre	A4 resp	rPTH resp
5	89.7	52.8	108.7	107.5	81.6	82.9	101.6	81.6	59.8	88.2	63.1	36.2	82.6
6	138.7	128	86	107.9	116.9	109.8	101.6	116.9	91	93	97.6	84	108.9
7	71.7	119.1	105.4	84.5	101.5	107.3	96.7	101.5	149.3	118.8	139.4	179.9	108.6
109	72.8	99.8	101.5	112	166.4	72.9	128.8	166.4	92.1	128.3	131.3	190.6	135.8
110	90.9	86.2	129.6	75.7	74.9	146.8	83.7	74.9	114.8	79.9	93	57.9	73.3
112	136.1	114.2	68.7	112.3	58.7	80.4	87.5	58.7	93.1	91.7	75.6	51.6	91
201	130.6	140.8	81.7	63.4	32.8	86.4	117.4	32.8	59.5	112.5	137.1	119.5	138.4
203	56.6	60.8	150.9	187.7	202.8	146.7	97.1	202.8	45.7	77.6	90.5	76.9	110.9
204	112.9	98.5	67.5	48.9	64.4	70	85.6	64.4	194.8	109.9	72.5	103.7	50.7

The data sets containing each subject's responsiveness to IGF-I/IGFBP-3 complex were then compared pairwise by calculating coefficients of correlation between the data sets. A density map of these correlations is shown in Figure 1 for 9602 and Figure 2 for 9604. Inspection of the density maps reveals a significant non-  
5 randomness to the distributions of density for each study. Correlations are observed to endocrine responsiveness within functional areas (somatotropic, adrenal, thyroid), suggesting that these kinds of statistical computations are valid and meaningful. Further, this method of representing endocrine responsiveness is novel and provides insights into the inter-connectivity between endocrine sub-systems.

10 The correlation between the responsiveness to three biochemical markers (IGF-I, IGFBP-3 and estradiol) is graphically represented in panels A-C of Figure 3. These graphs show that each subject appears to respond in a coordinate manner with respect to each of these biochemical indices. Similar connections were observed for other high density areas on the correlation maps.

15 In order to compute "effectiveness," the areas of density of the map with the highest interconnectiveness were chosen for further investigation. The somatotropic and bone group of biochemical markers, including C1CP, IGF-I, IGF-II, IGFBP-2, IGFBP-3, estradiol and erythropoietin (EPO) were chosen. For simplicity, a formula based on only the C1CP and IGFBP-3 responses was derived.

20 The working definition of drug efficacy for this example was the average of the data sets for the responses to C1CP and IGFBP-3 ("efficacy set"). Basal levels of various biochemical markers in the population in each study prior to receiving drug were compared in pairwise fashion with the efficacy set. All of those biochemical markers whose sets correlated (positively or negatively) with an "r" value exceeding  
25 0.4 were further investigated for inclusion as factors in a predictive relationship.



The data sets for basal levels of IGF-I, total T4 (tT4) and TSH were selected for further study. By empirical derivation using the procedure outlined above, the following formula (Formula #1) was derived:

5                    
$$P = \frac{\log ([TSH]+1) \times [tT4]}{[IGF-I]}$$

where,

P is the predicted efficacy of the drug

[TSH] is the basal concentration of TSH ( $\mu$ IU/mL)

10                    [tT4] is the basal concentration of total T4 (ng/mL)

[IGF-I] is the basal concentration of IGF-I (ng/mL).

The values utilized in this predictive method should lie within the normal clinical range. Any major derangement in a particular endocrine axis may prejudice the value of that biochemical marker in a predictive method. For the above factors, the normal clinical ranges are:

15

TSH: ca. 0.5-5.0  $\mu$ IU/mL.

tT4: ca. 40-130 ng/mL.

20                    IGF-I: ca. 70-440 ng/mL.

If a subject's value lies just outside the normal range for one of these factors, the closest boundary value within the normal range should be used in the computation.

25                    Figures 4 and 6 show part of the derivation of the above formula. In Fig. 3, only the TSH and tT4 values were utilized in the computation, leading to an "r" value of 0.843. This value was raised to 0.949 by including the [IGF-I] value in the computation.

The generality of this particular predictive method is shown by applying it to the data set from 9602. Despite vast differences in the populations used in the two studies (*i.e.*, age and gender), and in the mode of drug administration, the predictive method of Formula # 1 fits the data set of 9602 extremely well (Figure 5). It should also be mentioned that this predictive method can be used to predict either C1CP or IGFBP-3 responsiveness individually.

#### Example 2: Predictive Relationships for BMD, GS and FBM

Serum samples from Celtrix Pharmaceuticals' 9606 clinical study of rhIGF-I/IGFBP-3 for recovery from hip fracture were assayed and used to test and refine predictive methods. 24 elderly women (65-90 years of age) who had broken a hip were entered into the study immediately after surgical treatment of the fracture. The subjects were randomized into three groups to receive placebo (sodium acetate vehicle), 0.5 mg/kg/day rhIGF-I/IGFBP-3 ("low dose"), or 1 mg/kg/day rhIGF-I/IGFBP-3 ("high dose") by 24 hour subcutaneous infusion (administered with a portable minipump and reservoir). Each group received treatment for 8 weeks following hip fracture surgery. Hip bone mineral density (BMD), grip strength (GS) and fat body mass (FBM) were measured prior to the initiation of administration and four weeks after the end of the administration period (week 12). Blood samples were taken prior to the initiation of administration and at week 12, and serum was separated and reserved for analysis (although serum samples were not available from all subjects). Serum samples were assayed for the biochemical markers: IGF-I, IGF-II, IGFBP-2, IGFBP-3, ALS, total T4 (tT4), total T3 (tT3), TSH, 17-OH-progesterone, cortisol, DHEA, DHEAS, estradiol, testosterone, SHBG, LH, FSH, prolactin, erythropoietin,  $\alpha$ -fetoprotein, insulin C-peptide, IL-2, IFN- $\gamma$ , bone-specific alkaline protease, collagen C-peptide, osteocalcin, deoxypyridinoline, collagen N-telopeptide, and thyroglobulin.

As in the previous examples, relative response (12 week value vs. preadministration value) was calculated for each biochemical marker to minimize inter-subject variability. Additionally, relative responses for BMD, GS, and FBM were also calculated. BMD, GS and FBM relative responses were compared to  
 5 baseline values for each biochemical marker, and markers with regression coefficients (r values) > 0.4 (positive or negative) were selected for investigation as factors in a predictive relationship. Addition, multiplication, and division of the markers values, or the log of the marker values, were used to derive predictive relationships for prediction of relative response in BMD, DS and FBM. Any combinations of marker  
 10 values which resulted in a higher r value was selected for further refinement in an iterative process.

Formula #1 (see Example 1) was found to operate for GS (positive correlation) and FBM (negative correlation). A plot showing the data for GS in low dose (squares) and high dose (diamonds) patients is shown in Figure 7(A).

15 Formula # 1 was further refined for GS and FBM by incorporating an additional factor into the formula. Correlation with relative response in GS was found to be increased when Formula #1 was multiplied by the basal (preadministration) concentration of SHBG. The resulting formula (Formula #1-1),

$$20 \quad PE_{GS} \text{ or } PE_{FBM} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I]}$$

gives the predicted efficacy for GS ("PE<sub>GS</sub>") or FBM (PE<sub>FBM</sub>), where [TSH] is the basal concentration of TSH in  $\mu$ IU/ml, [tT4] is the basal concentration of tT4 in ng/ml, [SHBG] is the basal concentration of SHBG in nmol/liter, and [IGF-I] is the basal concentration of IGF-I in ng/ml.

25 Formula #1-2 was further refined for GS by dividing by the basal concentration of C1CP. The resulting formula (Formula #1-2),

$$PE_{GS} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I] \times [C1CP]}$$

gives  $PE_{GS}$ , where where [TSH] is the basal concentration of TSH in  $\mu IU/ml$ , [tT4] is the basal concentration of tT4 in ng/ml, [SHBG] is the basal concentration of SHBG in nmol/liter, [IGF-I] is the basal concentration of IGF-I in ng/ml, and [C1CP] is the basal concentration of C1CP in ng/ml. A plot of low dose (squares) and high dose (diamonds) patients is shown in Figure 7(B). Formula 1-2 was also applied to previous data sets (Celtrix studies 9602 and 9604). Correlations were excellent for 9604, but poor for 9602. The basis for this difference is unclear, and may relate to the different patient populations.

Formula 1 was also further refined for FBM by incorporating a different additional factor into the formula. Correlation with relative response was found to be increased when Formula #1 was multiplied by the basal concentration of SHBG divided by the basal concentration of tT3. The resulting formula (Formula #1-3),

$$PE_{FBM} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I] \times [tT3]}$$

gives the predicted efficacy for FBM (" $PE_{FBM}$ "), where [TSH] is the basal concentration of TSH in  $\mu IU/ml$ , [tT4] is the basal concentration of tT4 in ng/ml, [SHBG] is the basal concentration of SHBG in nmol/liter, [IGF-I] is the basal concentration of IGF-I in ng/ml, and [tT3] is the basal concentration of tT3 in ng/dl. A plot of low dose (squares) and high dose (diamonds) patients is shown in Figure 8(A).

A separate, new predictive relationship was derived for predicting BMD. Formula #2,

$$PE_{BMD} = \frac{[C1CP] \times [tT4]}{[tT3] \times [cort]}$$

gives the predicted efficacy for hip bone density (" $PE_{BMD}$ "), where [C1CP] is the basal concentration of C1CP in ng/ml, [tT4] is the basal concentration of tT4 in ng/ml, [tT3] is the basal concentration of tT3 in ng/dl, and [cort] is the basal concentration of cortisol in  $\mu g/dl$ .

The predictive relationships were further tested by comparing the  $r$  values of data from low and high dose patient groups, shown in Table 3. The same comparison is shown graphically in Figures 7(A), 7(B), 8(A) and 8(B) for some of the formulae, with separate regression lines drawn for the low and high dose data sets.

5

Table 3

<u>Formula</u>	<u>Low Dose (n=6)</u>	<u>High Dose (n=8)</u>	<u>Combined (n=14)</u>
Formula #1	0.97	0.73	0.76
Formula #1-1(GS)	0.83	0.88	0.81
Formula #1-1(FBM)	-0.93	-<0.4	-0.53
Formula #1-2	0.81	0.94	0.93
Formula #1-3	-0.92	-0.75	-0.82
Formula #3	<0.4	0.84	0.75

10

The comparison of the regression analyses for the low and high doses was highly informative, and was the basis for a new method of analysis of dose responsiveness. The calculated lines for the  $PE_{BMD}$  from Formula #3 are not at all similar, but the calculated lines for  $PE_{GS}$  from Formula #1-2 are (Figure 7(B) shows that the calculated lines for  $PE_{GS}$  are nearly coincident). It has been shown in preclinical studies BMD response to rhIGF-I/IGFBP-3 increases through a broad range, with greater responses seen at high doses (Bagi et al., 1995, *Calcif. Tissue Int.* 57(1):40-46).

15

The patents, patent applications, and publications cited throughout the disclosure are incorporated by reference herein in their entirety.

The present invention has been detailed both by direct description and by example. Equivalents and modifications of the present invention will be apparent to those skilled in the art, and are encompassed within the scope of the invention.

20

I claim:

10

15

20

25

measuring the subject's serum level of procollagen peptide ("[C1CP]"); and calculating said subject's responsiveness by the formula

$$PE_{GS} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I] \times [C1CP]}$$

5 wherein [TSH] is the basal concentration of TSH in  $\mu$ IU/ml, [tT4] is the basal concentration of tT4 in ng/ml, [SHBG] is the basal concentration of SHBG in nmol/liter, [IGF-I] is the basal concentration of IGF-I in ng/ml, and [C1CP] is the basal concentration of C1CP in ng/ml.

10 3. A method for predicting the effect of the administration of insulin-like growth factor I (IGF-I) on fat body mass ( $PE_{FBM}$ ) in a subject, comprising:

measuring the subject's serum level of thyroid stimulating hormone ("[TSH]");

measuring the subject's serum level of total tetraiodothyronine ("[tT4]");

15 measuring the subject's serum level of sex hormone binding globulin ("[SHBG]");

measuring the subject's serum level of IGF-I ("[IGF-I]");

measuring the subject's serum level of total triiodothyronine ("[tT3]"); and

calculating said subject's responsiveness by the formula

20 
$$PE_{FBM} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I] \times [tT3]}$$

wherein [TSH] is the basal concentration of TSH in  $\mu$ IU/ml, [tT4] is the basal concentration of tT4 in ng/ml, [SHBG] is the basal concentration of SHBG in nmol/liter, [IGF-I] is the basal concentration of IGF-I in ng/ml, and [tT3] is the basal concentration of tT3 in ng/dl.

25

4. A method for predicting the effect of the administration of insulin-like growth factor I (IGF-I) on hip bone mineral density ( $PE_{BMD}$ ) in a subject, comprising:

measuring the subject's serum level of procollagen peptide ("[C1CP]");  
 measuring the subject's serum level of total tetraiodothyronine ("[tT4]");  
 measuring the subject's serum level of total triiodothyronine ("[tT3]");  
 measuring the subjects seru level of cortisol ("[cort]"); and  
 5 calculating said subject's responsiveness by the formula

$$PE_{BMD} = \frac{[C1CP] \times [tT4]}{[tT3] \times [cort]}$$

wherein [C1CP] is the basal concentration of C1CP in ng/ml, [tT4] is the  
 basal concentration of tT4 in ng/ml, [tT3] is the basal concentration of tT3 in  
 10 ng/dl, and [cort] is the basal concentration of cortisol in µg/dl.

5. A diagnostic kit for predicting a subject's responsiveness to an insulin-like  
 growth factor I (IGF-I) drug or treatment regiment, comprising:

at least one set of reagents for measuring biochemical parameters,  
 15 resulting in at least one biochemical value; and

a means for utilizing one or more biochemical values to predict the  
 subject's responsiveness to said IGF-I drug or treatment regimen,  
 wherein said biochemical parameters are selected from the group consisting of serum  
 thyroid stimulating hormone ("[TSH]"), total serum tetraiodothyronine ("[tT4]"),  
 20 serum sex hormone binding globulin ("[SHBG]"), serum IGF-I ("[IGF-I]"), total  
 serum triiodothyronine ("[tT3]"), serum cortisol ("[cort]"), and serum procollagen  
 peptide ("[C1CP]"), and said predictive relationship is selected from the group  
 consisting of

$$25 \quad PE_{GS} \text{ or } PE_{FBM} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I]},$$

$$PE_{GS} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I] \times [C1CP]},$$

$$PE_{BMD} = \frac{[C1CP] \times [tT4]}{[tT3] \times [cort]}, \text{ and}$$



$$PE_{FBM} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I] \times [tT3]}$$

6. The diagnostic kit of claim 5 wherein said predictive relationship is

5 
$$PE_{GS} \text{ or } PE_{FBM} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I]}$$

7. The diagnostic kit of claim 5 wherein said predictive relationship is

10 
$$PE_{GS} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I] \times [C1CP]}$$

8. The diagnostic kit of claim 5 wherein said predictive relationship is

15 
$$PE_{BMD} = \frac{[C1CP] \times [tT4]}{[tT3] \times [cort]}$$

9. The diagnostic kit of claim 5 wherein said predictive relationship is

$$PE_{FBM} = \frac{\log(1+[TSH]) \times [tT4] \times [SHBG]}{[IGF-I] \times [tT3]}$$

20 10. A method for determining equivalence of a first and a second dosage of a drug for a response, comprising:

measuring biochemical parameters from a first and second cohort of subjects, thereby obtaining biochemical values;

25 administering the first dosage of the drug to said first cohort of subjects;

administering the second dosage of the drug to said second cohort of subjects;

measuring responses to said first and second dosages in the first and second cohorts, thereby obtaining response values;

calculating predicted response values to said drug utilizing a predictive relationship, said biochemical values, and said response values for each of said first and second cohorts;

5 performing linear regression analysis on said predicted response values and said response values for each of said first and second cohorts;

comparing said linear regression analysis of said first cohort with the linear regression analysis of said second cohort; and

determining if the first and second dosages are equivalent with respect to the response.

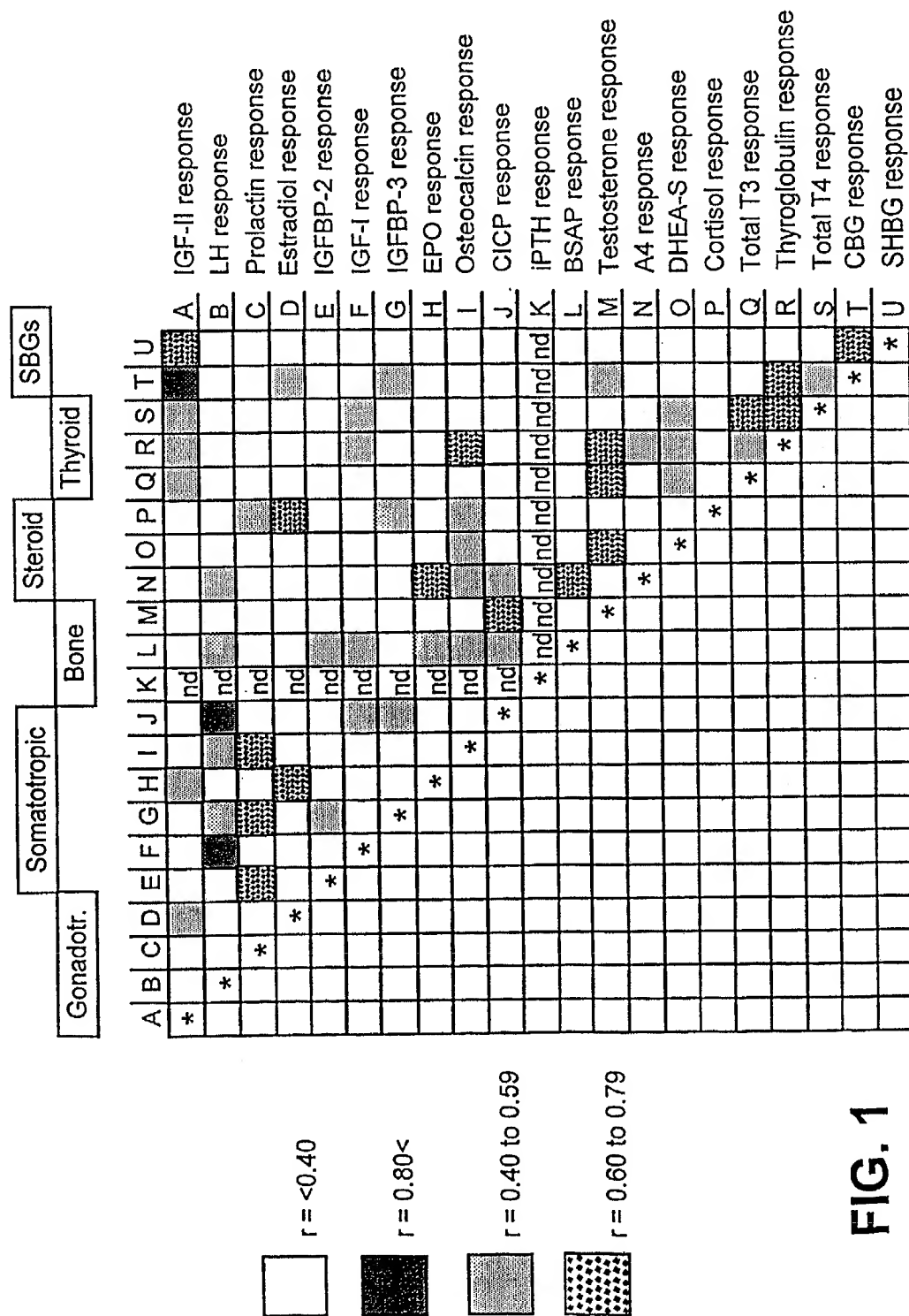


FIG. 1

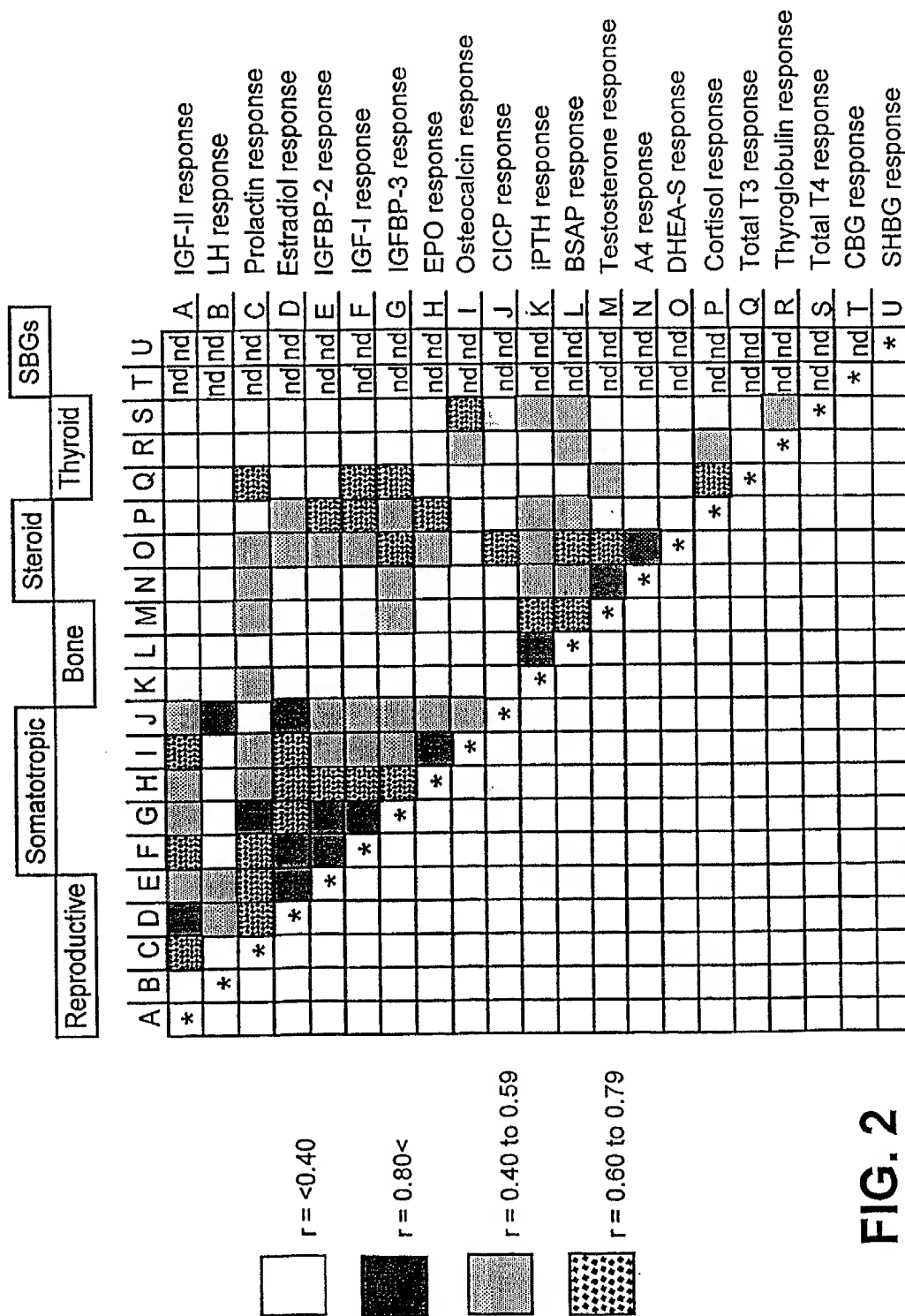
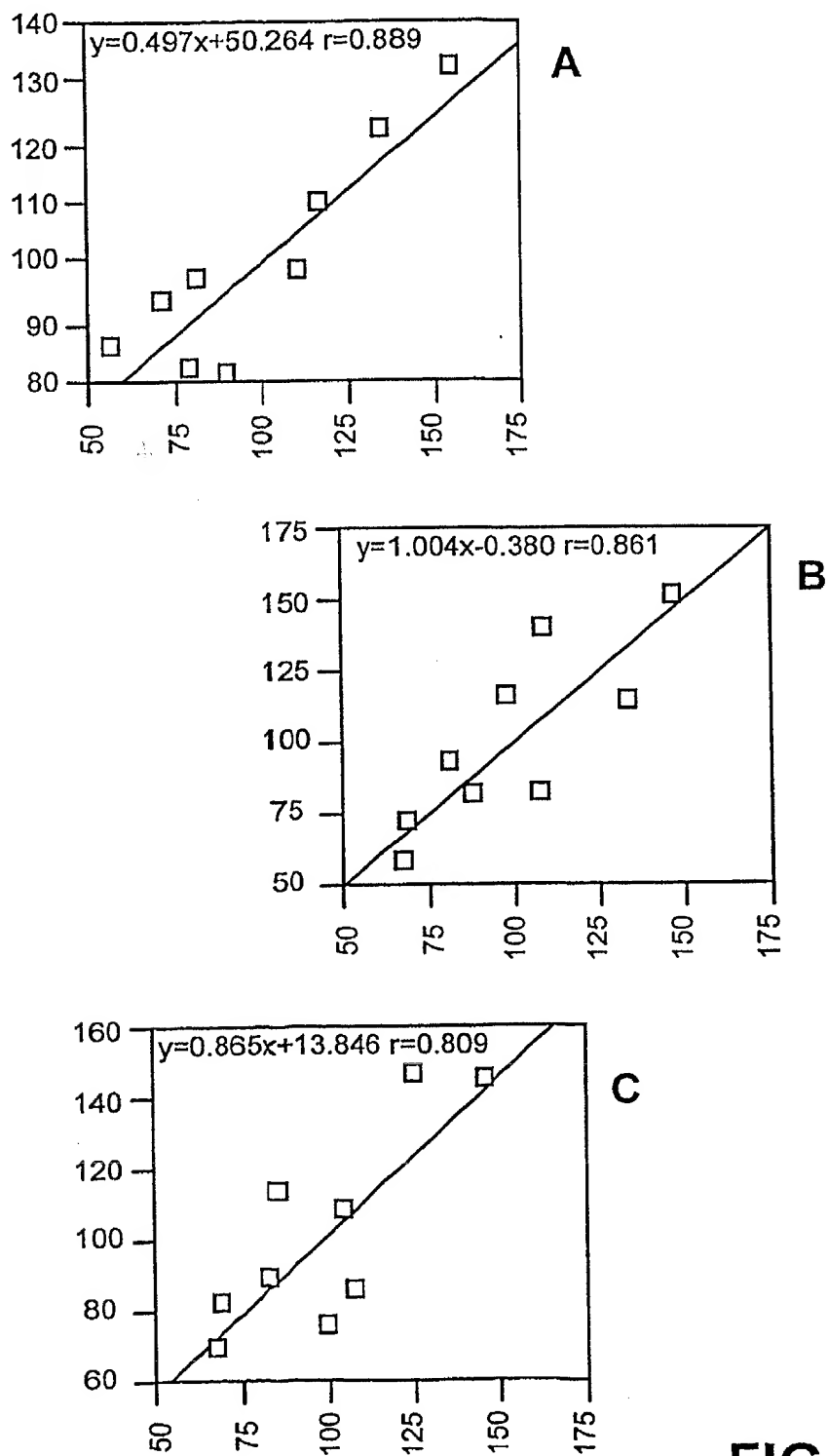


FIG. 2

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**FIG. 3**

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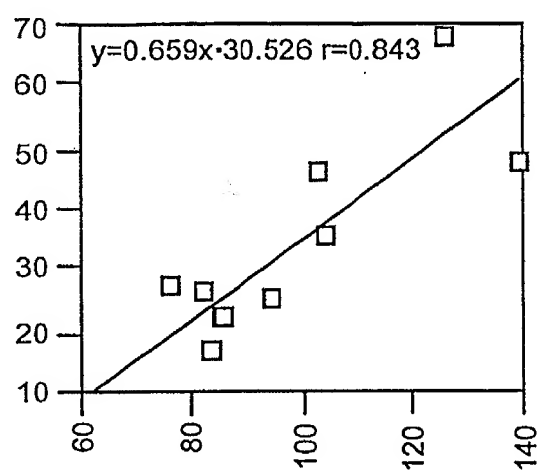


FIG. 4

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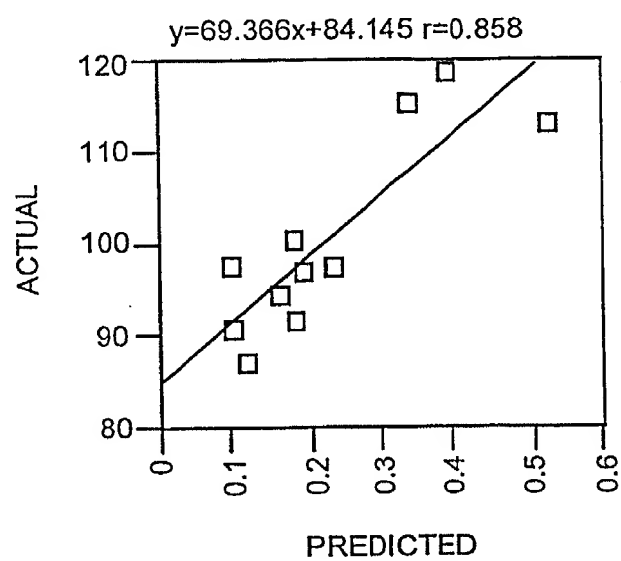


FIG. 5

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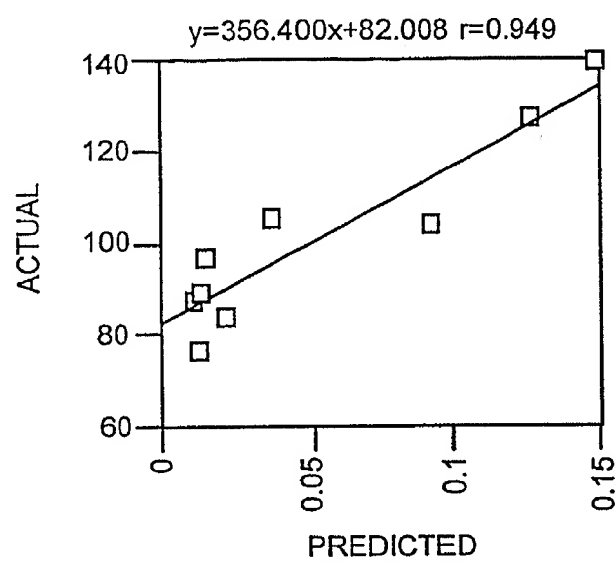
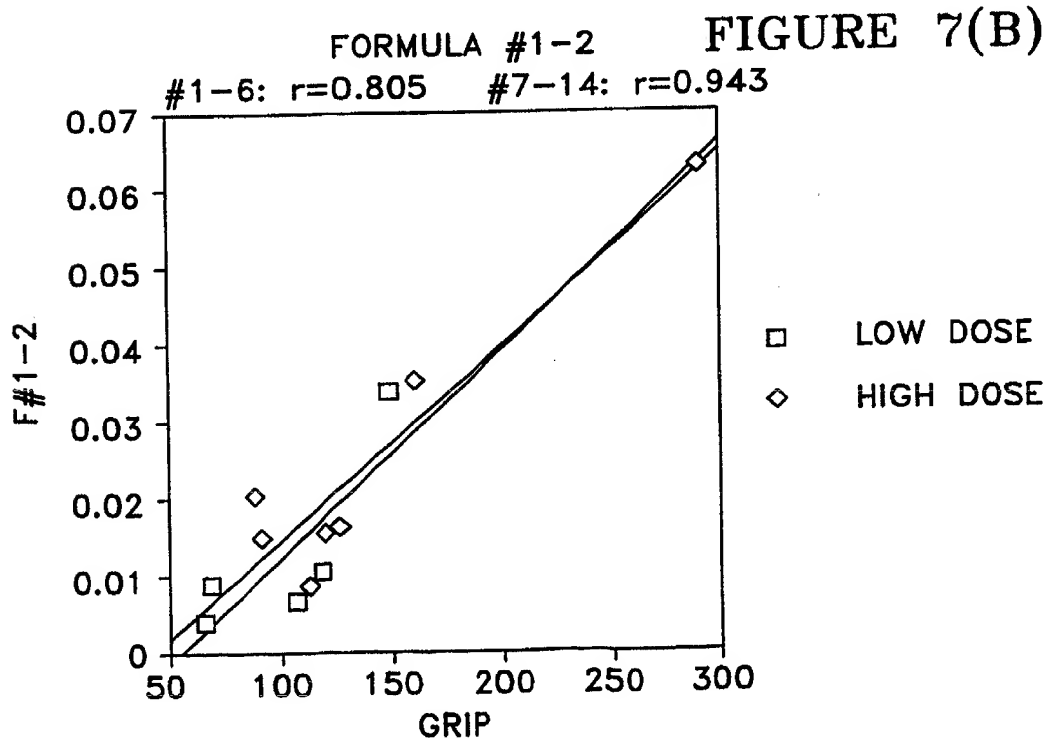
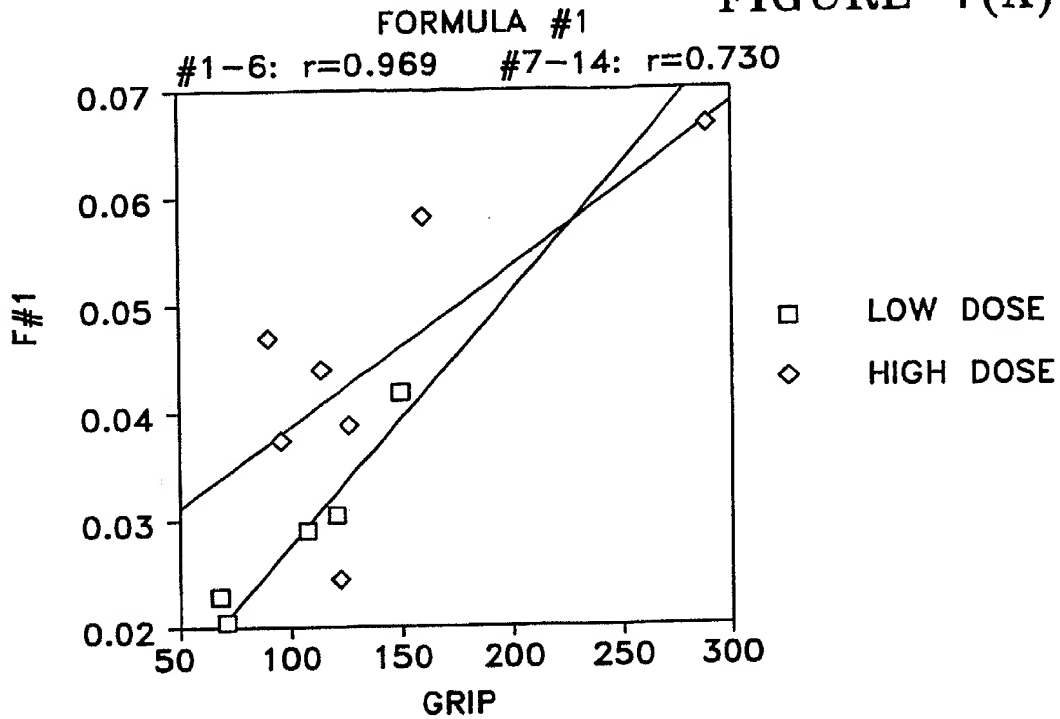


FIG. 6



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FIGURE 7(A)



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FIGURE 8(A)

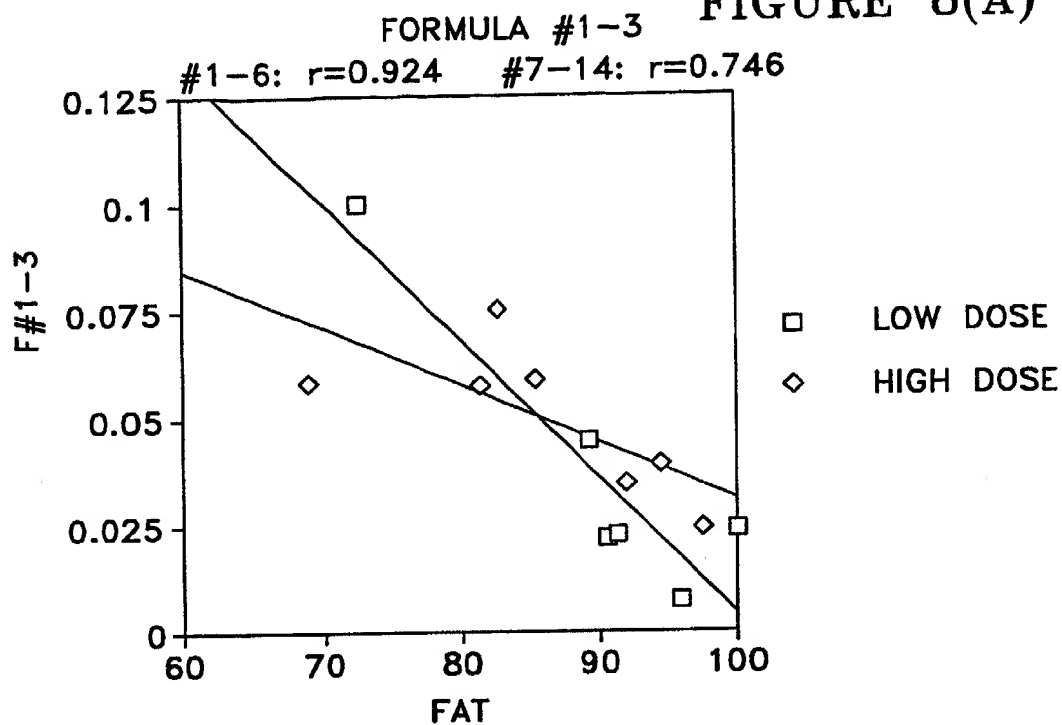
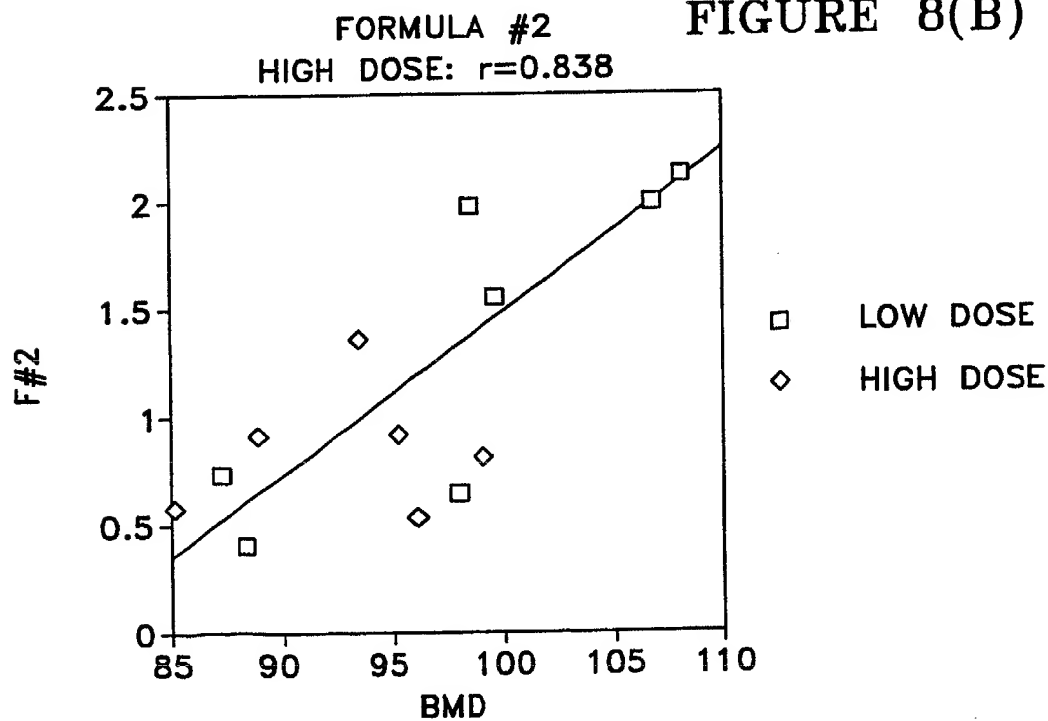


FIGURE 8(B)



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<b>(21) International Application Number:</b> PCT/US99/17103 <b>(22) International Filing Date:</b> 27 July 1999 (27.07.99)  <b>(30) Priority Data:</b> 09/123,050      27 July 1998 (27.07.98) <b>US</b>  <b>(71) Applicant:</b> CELTRIX PHARMACEUTICALS, INC. [US/US]; Suite 600, 2033 Gateway Place, San Jose, CA 95110 (US).  <b>(72) Inventor:</b> MASCARENHAS, Desmond; 27233 Sherlock Road, Los Altos, CA 94022 (US).  <b>(74) Agents:</b> BUFFINGER, Nicholas, S. et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).		<b>(81) Designated States:</b> AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>  <b>(88) Date of publication of the international search report:</b> 23 November 2000 (23.11.00)
<b>(54) Title:</b> METHODS FOR PREDICTING DRUG RESPONSE, IN PARTICULAR IGF-I  <b>(57) Abstract</b>  Methods are provided for predicting the response of a subject to a drug or treatment regimen. The predictive measurement is used with biochemical parameters obtained from a subject to predict whether that subject will respond to the particular drug or treatment regimen. Predictive methods may also be used to determine the equivalence of different dosages of a drug.		

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/17103

A. CLASSIFICATION OF SUBJECT MATTER  
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According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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P,A	WO 98 37423 A (MASCARENHAS DESMOND ;CELTRIX PHARMA (US)) 27 August 1998 (1998-08-27) the whole document	1-5
A	ROELEN, CORNE A. M. ET AL: "High-affinity growth hormone (GH)-binding protein (GHP), body fat-- mass, and insulin - like growth factor-binding protein- predict the GHP response to GH therapy in adult GH deficiency syndrome." METABOLISM CLINICAL AND EXPERIMENTAL, (MARCH, 1999) VOL. 48, NO. 3, PP. 314-318., XP000892210 abstract	1-5

☒ Further documents are listed in the continuation of box C.

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International Application No  
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A	US 5 593 844 A (CARLSSON LENA M S ET AL) 14 January 1997 (1997-01-14) column 37, line 50 -column 38, line 14 ---	1-5
A	WO 97 38709 A (PHARMACIA & UPJOHN AB ;JOHANNSSON GUDMUNDUR (SE); MAARIN PER (SE);) 23 October 1997 (1997-10-23) tables 2,4 ---	1-5
A	US 5 407 927 A (MORALES ARLENE J ET AL) 18 April 1995 (1995-04-18) figure 4; table 1 -----	1-5

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 99/17103

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 10  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

**1. Claims: 1-9**

Methods for determining the effect of the administration of Igf-I, Kit therefor.

**2. Claim : 10**

Method for determining the equivalence of first and second dosages of a drug.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 10

Claim 10 contains insufficient technical features for a meaningful search to be performed. Reference is made to "measuring biochemical parameters" but none are specified. The claim is thus flawed under Article 6 PCT and a meaningful search is hence not possible (Article 17(2)(a)(ii) and (b) PCT).

Furthermore there is a question of non-patentability with respect to Rule 39.1(iv), PCT: methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, and Rule 39.1(i), PCT: scientific and mathematical theories.

Consequently the subject matter of claim 10 cannot be considered for international search according to Article 17(2)(a)(i) and (b) PCT in combination with Rule 39.1(iv)(i) PCT.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/17103

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US 5593844 A	14-01-1997	US 5210017 A AU 657109 B DE 69119911 D DE 69119911 T EP 0558647 A GR 3020505 T HK 1007351 A JP 2977280 B JP 6502724 T AT 138739 T AU 9106791 A CA 2093927 A DK 558647 T EP 0681842 A EP 0995445 A ES 2090598 T JP 11346765 A WO 9208985 A	11-05-1993 02-03-1995 04-07-1996 21-11-1996 08-09-1993 31-10-1996 09-04-1999 15-11-1999 24-03-1994 15-06-1996 11-06-1992 20-05-1992 19-08-1996 15-11-1995 26-04-2000 16-10-1996 21-12-1999 29-05-1992
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